



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>5</sup> :</b> <b>A61K 39/395, 43/00, C12N 15/02</b> <b>C12P 21/08</b>	<b>A3</b>	<b>(11) International Publication Number:</b> <b>WO 94/11026</b> <b>(43) International Publication Date:</b> <b>26 May 1994 (26.05.94)</b>
<b>(21) International Application Number:</b> <b>PCT/US93/10953</b> <b>(22) International Filing Date:</b> <b>12 November 1993 (12.11.93)</b>  <b>(30) Priority data:</b> <b>07/978,891 13 November 1992 (13.11.92) US</b> <b>08/149,099 03 November 1993 (03.11.93) US</b>  <b>(71) Applicant:</b> <b>IDEC PHARMACEUTICALS CORPORATION [US/US]; 11011 Torreyana Road, San Diego, CA 92121-1104 (US).</b>  <b>(72) Inventors:</b> <b>ANDERSON, Darrell, R. ; 1851 Navato Place, Escondido, CA 92029 (US). RASTETTER, William, H. ; 16067 Puerta Del Sol, Rancho Santa Fe, CA 92067 (US). HANNA, Nabil ; 3255 Fortuna Ranch Road, Olivenhain, CA 92024 (US). LEONARD, John, E. ; 1960 Avenida Joaquin, Encinitas, CA 92024 (US). NEWMAN, Roland, A. ; 43111 Robbins Street, San Diego, CA 92122 (US). REFF, Mitchell, E. ; 4166 Combe Way, San Diego, CA 92122 (US).</b>		<b>(74) Agents:</b> <b>WEISS, Steven, M. et al.; Lyon &amp; Lyon, 611 West Sixth Street, 34th Floor, Los Angeles, CA 90017 (US).</b>  <b>(81) Designated States:</b> <b>AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</b>  <b>Published</b> <i>With international search report.</i>  <b>(88) Date of publication of the international search report:</b> <b>18 August 1994 (18.08.94)</b>
<b>(54) Title:</b> <b>THERAPEUTIC APPLICATION OF CHIMERIC AND RADIOLABELED ANTIBODIES TO HUMAN B LYMPHOCYTE RESTRICTED DIFFERENTIATION ANTIGEN FOR TREATMENT OF B CELL LYMPHOMA</b>  <b>(57) Abstract</b>  Disclosed herein are therapeutic treatment protocols designed for the treatment of B cell lymphoma. These protocols are based upon therapeutic strategies which include the use of administration of immunologically active mouse/human chimeric anti-CD20 antibodies, radiolabeled anti-CD20 antibodies, and cooperative strategies comprising the use of chimeric anti-CD20 antibodies and radiolabeled anti-CD20 antibodies.		

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<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 5    A61K39/395    A61K43/00    C12N15/02    C12P21/08		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC 5    C07K    A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 274 394 (INTERNATIONAL GENETIC ENGINEERING, INC (INGENE)) 13 July 1988 cited in the application see page 9, line 22 - line 37 see page 13, line 8 - line 44 ---	1
X	JOURNAL OF IMMUNOLOGY vol. 139, no. 10, 15 November 1987, BALTIMORE US pages 3521 - 3526 ALVIN Y. LIU ET AL. 'PRODUCTION OF A MOUSE-HUMAN CHIMERIC MONOCLONAL ANTIBODY TO CD20 WITH POTENT FC-DEPENDENT BIOLOGIC ACTIVITY.' cited in the application see the whole document -----	1
<input type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&amp;" document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search  <div style="text-align: center; font-weight: bold;">19 April 1994</div>	Date of mailing of the international search report  <div style="text-align: center; font-weight: bold;">20. 05. 94</div>	
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer  <div style="text-align: center; font-weight: bold;">Rempp, G</div>	

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark : Although claims 1 to 10, 16 to 20 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0274394	13-07-88	AU-B- 606653	14-02-91
		AU-A- 1189188	27-07-88
		JP-T- 2503143	04-10-90
		WO-A- 8804936	14-07-88
		ZA-A- 8800091	27-06-88
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**H. CLAIMS**

What is claimed is:

- 5 1. A method for the treatment of B cell lymphoma comprising the step of administering a therapeutically effective amount of at least one immunologically active, chimeric anti-CD20 antibody to a human.
2. The method of claim 1 wherein the amount of said antibody administered  
10 to said human is between about 0.001 to about 30 milligrams of antibody per kilogram body weight of said human ("mg/kg").
3. The method of claim 1 wherein said antibody is derived from a  
transfectoma comprising anti-CD20 in TCAE 8 as deposited with the American  
15 Type Culture Collection as part of ATCC deposit number 69119.
4. The method of claim 1 further comprising the step of administering a  
second therapeutically effective amount of at least one immunologically active,  
chimeric anti-CD20 antibody.  
20
5. The method of claim 4 wherein said additional administration of said  
antibody to said human occurs within about seven days of said first  
administration of said antibody to said human.
- 25 6. A method for the treatment of B cell lymphoma comprising the steps of:
  - 1) administering, at a first administration period, a first therapeutically effective amount of immunologically active, chimeric anti-CD20 antibody to a human;

2) administering at a second subsequent administration period, a second therapeutically effective amount of said antibody;

3) administering, at a third subsequent administration period, a third therapeutically effective amount of said antibody.

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7. The method of claim 6 wherein said first, second and third therapeutically effective amount of said antibody is between about 0.001 mg/kg to about 30 mg/kg.

10 8. The method of claim 6 wherein said second administration period is within about seven days of said first administration period.

9. The method of claim 6 wherein said third administration period is within about fourteen days of said first administration period.

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10. The method of claim 6 wherein said antibody is derived from a transfectoma comprising anti-CD20 in TCAE 8 (within ATCC deposit number 69119).

20 11. Immunologically active, chimeric anti-CD20 produced from a transfectoma comprising anti-CD20 in TCAE 8 (within ATCC deposit number 69119).

12. A hybridoma which secretes anti-CD20 antibody, said hybridoma being identified by American Type Culture Collection deposit number HB 11388.

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13. A monoclonal antibody secreted from the hybridoma of claim 12.

14. A radiolabeled antibody according to claim 12.

15. The radiolabeled antibody of claim 14 where the radiolabel is selected from the group consisting of yttrium [90]; indium [111], and iodine [131].
16. A method for the treatment of B cell lymphoma comprising of steps of  
5 administering a therapeutically effective amount of the antibody of claim 14 to a human.
17. The method of claim 16 when the radiolabel of said antibody is yttrium [90].
- 10 18. A method for the treatment of B cell lymphoma comprising the steps of:
- 1) administering, at a first administration period, an immunology active chimeric anti-CD20 antibody to human; and
- 15 2) administering, at a second administration period, a radiolabeled anti-CD20 antibody to said human.
19. The method of claim 18 when said chimeric anti-CD20 is derived from a  
20 transfectoma comprising anti-CD20 in TCAE 8 as deposited with the American Type Culture Collection as part of ATCC deposit number 69119.
20. The method of claim 8 when said radiolabeled antibody comprises a monoclonal antibody secreted from a hybridoma identified by American Type  
25 Culture Collection deposit number HB 11388.